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A New Peptide Coupling Reagent—Dialkyl Phosphite

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Eighteen N-protected dipeptide esters were synthesized using dialkyl phosphite as a coupling reagent. The reaction proceeded probably through a mixed carboxylic–phosphoric anhydride intermediate. The dipeptide esters were prepared in satisfactory yields and low racemization.

In 1941, F. Lipmann (*1*) proposed that protein biosynthesis proceeded through a mixed carboxylic–phosphoric anhydride intermediate. Since then a variety of organophosphorus compounds have been developed as peptide coupling reagents (*2*). However, only a few of the coupling reactions proceeded through a mixed carboxylic–phosphoric anhydride intermediate. In these reactions the dialkyl or diaryl phosphorochloridates were used as activating reagents (*3–8*) but these dialkyl or diaryl phosphorochloridates reagents are not stable enough and often turn yellowish. We tried to solve this problem using dialkyl phosphite to generate the phosphorochloridates *in situ* for the phosphorylation reaction.

In a previous paper (*9*), we described the phosphorylation of amino acids in which the *N*-(dialkoxyphosphoryl)dipeptides were formed as by-products that might be due to the presence of excess dialkyl phosphite, leading to the coupling reaction. Thus, dialkyl phosphite has potential as a coupling reagent. In this paper, a series of dipeptides was synthesized by this novel method.

In the presence of triethylamine and carbon tetrachloride, the dialkyl phosphite **1** was probably transformed *in situ* into a dialkyl phosphorochloridate **2** (*10*) which phosphorylated the N-protected amino acid **3** or **7** immediately to give the mixed carboxylic–phosphoric anhydride **4** or **8** (*11, 12*). Following the nucleophilic attack by amino acid ester, the reaction resulted in the formation of the N-protected dipeptide **6** or **9** (Schemes A and B). The experiment was carried out by the addition of 1.1 eq of dialkyl phosphite to a solution of *N*-(diisopropyloxyphosphoryl)amino acid (*N*-DIPP-amino acid) (2 mmol) in methylene dichloride (15 ml) (or other organic solvent such as THF or DMF) containing 2 eq of triethylamine and carbon tetrachloride (10 ml) within 10 min at 0°C. The mixture was stirred at 0°C for 2–4 h. Then, an additional 2 eq of triethylamine with 1.1 eq of amino acid ester hydrochloride salt was added. The final solution was stirred at room temperature for 2–4 h. The solution was washed with dilute citric acid solution and saturated sodium bicarbonate and water. The organic layer was dried and evaporated *in vacuo* to dryness. In most cases, the products at this stage could be

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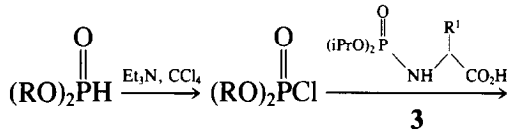
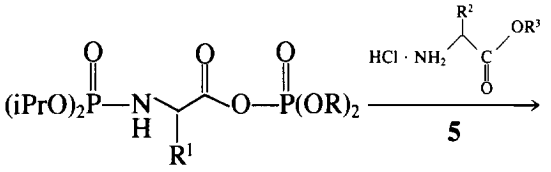
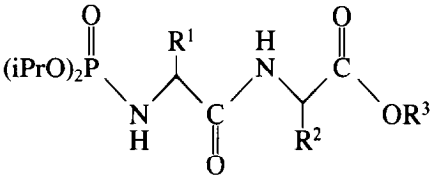


1a, 1b, 1c, 1d **2a, b, c, d**



4a, b, c, d



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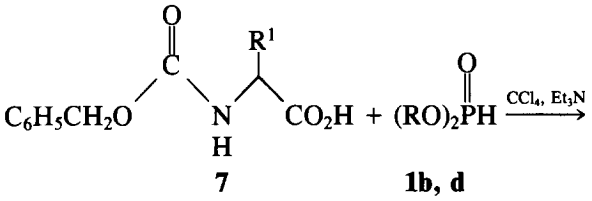
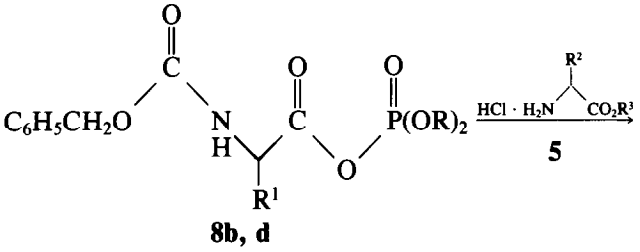
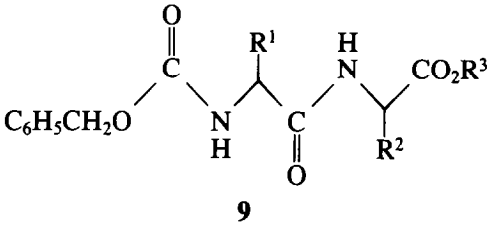
R = Methyl, Ethyl, Isopropyl, Butyl
a **b** **c** **d**

SCHEME A

obtained in pure state and were detected by thin-layer chromatography and spectroscopic analysis. ^{31}P NMR spectroscopic analysis shows that no phosphoramidates are generated as by-products in the reaction. The major impurities are phosphates and pyrophosphates. Satisfactory microanalysis was obtained after one recrystallization or several washings with petroleum ether. If the product was oil, chromatographic purification was necessary. The *N*-(diisopropyloxyphosphoryl)dipeptide esters **6a–6g** (*N*-DIPP-dipeptide esters) were isolated in yields of 68–92%. Table 1 gives the physical properties of *N*-(diisopropyloxyphosphoryl)dipeptide esters **6a–6g** and benzoyl butyl amide **10** synthesized by this method. The structures of these products were determined by ^{31}P NMR, ^{1}H NMR, ^{13}C NMR, fast atom bombardment–mass spectrometry (FAB–MS), ir spectrometry, and elemental analysis (Tables 1 and 2). The ^{31}P NMR chemical shifts of dipeptides **6a, 6b, 6d,** and **6e** are in the range 5.3 ± 0.2 ppm. For compounds (**6c, 6f, 6g**) in which the N-terminal amino acids are proline and glycine, the ^{31}P NMR chemical shifts are in the range 6.3 ± 0.2 ppm. The ^{13}C NMR peaks of the amide group's carbon and the β_1 carbon in the R^1 group are split into a doublet by the phosphorus atom. In addition, the dipeptides give a fragmentation pattern for positive-ion FAB–MS similar to that of the analogs reported in a previous paper (*9*). The *N*-(diisopro-







SCHEME B

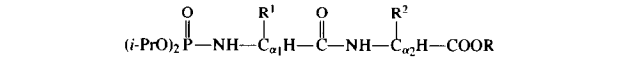
TABLE 1

Physical Properties of *N*-DIPP-dipeptide Esters

Entry	Compound	Active reagent	Yield (%)	mp (°C)	$[\alpha]_D$ ($CHCl_3$) 30°C	FAB–MS $(M + H)^+$	ir (cm^{-1})
6a	DIPP-L-Ala-L-Phe-OMe	DMPH	74	87–88	+9.89 *C* = 4.6	415	1685, 1750
		DEPH	75	86–88	+9.86 *C* = 3.7	—	—
		DIPPH	72	87–88	+6.50 *C* = 1.0	—	—
		DBPH	68	87–88	+7.27 *C* = 1.1	—	—
6b	DIPP-L-Ala-L-Tyr-OMe	DMPH	87	171–172	+10.0 *C* = 0.7	431	1640; 1730
6c	DIPP-Gly-Gly-OEt	DMPH	77	Oil	—	325	1665; 1740
6d	DIPP-L-Phe-Gly-OEt	DCC + NHS	84	107–108	−28.2 *C* = 1.0	415	1650; 1745
		DCC	81	107–108	−28.2 *C* = 1.0	415	1650; 1745
		DMPH	74	107–108	−25.5 *C* = 1.0	—	—
		DEPH	76	107–108	—	—	—
		DBPH	72	107–108	−26.2 *C* = 1.0	415	1660; 1750
6e	DIPP-L-Phe-L-Tyr-OMe	DMPH	90	40–41	+18.9 *C* = 1.8	507	1645; 1740
6f	DIPP-L-Pro-Gly-OEt	DMPH	81	Oil	—	365	1680; 1750
		DEPH	72	Oil	—	365	1680; 1750
		DIPPH	78	Oil	—	—	1680; 1750
		DBPH	73	Oil	−24.0 *C* = 0.5	365	1680; 1750
6g	DIPP-L-Pro-L-Tyr-OMe	DMPH	92	91–92	−26.8 *C* = 1.4	457	1670; 1740
10	PbC(O)NHBu	DBPH	76	37.5–38	—	178	1630
11	Bz-Leu-Gly-OEt	DMPH	78	—	−31.2 *C* = 3.1 (EtOH)	—	—
		DEPH	85	—	−32.0 *C* = 3.1 (EtOH)	—	—
		DIPPH	82	—	−30.0 *C* = 3.1 (EtOH)	—	—
		DBPH	89	—	−32.4 *C* = 3.1 (EtOH)	—	—

TABLE 2

^{13}C and ^{31}P NMR Chemical Shifts (ppm) and Coupling Constants (Hertz in Parentheses) of DIPP-dipeptide Esters



Entry	Compound	^{31}P NMR	^{13}C NMR					
			C(O)-N	COOR	C_{α_1}	C of R^1	C_{α_2}	C of R^2
6a	DIPP-DL-Ala-L-Phe-OMe	5.3	172.3(7.3)	170.9	50.1	19.9(4.4)	5.24	36.7; 36.8; 135.3; 135.8
		5.4	172.5(5.8)	170.8			52.6	128.1; 127.3; 125.8
	DIPP-L-Ala-L-Phe-OMe	5.4(DMPH)				—		
		5.4(DEPH)				—		
		5.4(DIPPH)				—		
		5.51(DBPH)				—		
6b	DIPP-L-Ala-L-Tyr-OMe	5.2	173.4(5.9)	171.8	50.4	20.7	53.7	156.1; 129.9; 126.7; 115.0; 36.2
6c	DIPP-Gly-Gly-OEt	6.1	172.3(8.8)	169.2	44.3		40.7	
6d	DIPP-L-Phe-Gly-OEt	5.3	172.8(4.4)	169.2	56.7	39.5(4.4); 136.7; 129.5; 128.2; 126.5	41.0	
6e	DIPP-L-Phe-L-Tyr-OMe	5.1	171.7(4.4)	171.2	56.4	136.1; 129.4; 128.3; 125.9; 39.1	53.4	156.0; 129.8; 126.6; 115.3; 36.9
6f	DIPP-L-Pro-Gly-OEt	6.5	17.3(0)	169.0	61.0	30.1(5.8); 25.0(5.8); 47.6	41.1	
6g	DIPP-L-Pro-L-Tyr-OMe	6.3	172.7(0)	171.3	61.3	30.5(4.4); 24.6(5.9); 47.4	53.1	115.3; 36.9; 156.1; 129.7; 126.2;
10	PhC(O)NHBu	—	170.2			136.9; 133.2; 130.4; 129.4		42.1; 33.8; 22.3; 15.9

pyloxyphosphoryl)dipeptide esters were dominated by the C_{α_1}—C=O scission followed by the loss of two molecules of propylene to give the relatively stable *N*-(phosphoryl)iminium ion as the base peak (*9*).

Using dicyclohexylcarbodiimide (DCC) and DCC with *N*-hydroxysuccinimide (NHS) to synthesize the dipeptide ester **6d,** we found that the by-product dicyclohexylurea (DCU) was present in organic solvent. After evaporation of the solvent, a mixture of dipeptide and DCU was obtained. The crude dipeptide ester must be recrystallized several times. In a comparison of this dialkyl phosphite method to the DCC and DCC with NHS methods, the advantage is that the by-product dialkyl phosphate could be easily removed by washing with aqueous sodium bicarbonate. On the other hand, the DCU may be removed completely by several recrystallizations.

Other types of N-protected dipeptide esters, *N*-(benzyloxycarbonyl)dipeptide esters (*N,Z*-dipeptide esters) **9a–9j** and *N*-(benzoyl)dipeptide ester **11,** were also synthesized by this dialkyl phosphite method. Table 3 shows that the yields of the products of *N*-(benzyloxycarbonyl)dipeptide esters **9a–9j** are 76–88%, which are comparable to those of the solution synthesis of peptides, and the optical purity of products is comparable with that of dipeptides reported in the literature (*13–18*).

It is worthwhile to note from Tables 1 and 3 that all dialkyl phosphites give similar results, indicating that steric hindrance does not hamper the final yield so long as the reaction conditions are chosen properly.

To clarify the extent of racemization for this procedure, the standardized Young method (*19*) was used. The model compound *N*-benzoyl-leucine–glycine ethyl ester **11** was synthesized using dialkyl phosphites as coupling reagents. The mea-

TABLE 3

Yields and Physical Properties of the Synthetic *N,Z*-Dipeptide Esters or Amides **9a–9j**

Entry	Compound[a]	Active reagent	Yield (%)	FAB–MS	mp (°C) [Lit. mp]	$[\alpha]_D^{25}(C = 1)$ [Lit. $[\alpha]_D$]
9a	*Z*-Ala-Ala-OMe	DEP	83	309	104–106 [104–105] [13]	−53.5(MeOH) [13] [−53(MeOH)]
9b	*Z*-Ala-Gly-OEt	DEP	78	309	95–97 [97–98] [14]	−23.5(EtOH) [14] [−24(EtOH)]
9c	*Z*-Leu-Gly-OMe	DEP	80	337	92–94 [92–93] [15]	−26.5(MeOH) [15] [−26(MeOH)]
9d	*Z*-Pro-Ala-OBzl	DBP	76	411	95–97	+32.0(MeOH)
9e	*Z*-Pro-Gly-OEt	DBP	80	335	60–62	−25.0(MeOH)
9f	*Z*-Pro-Leu-OMe	DEP	83	377	74–75 [74–75) [16]	−44.0(DMF) [16] [−42.5(DMF)]
9g	*Z*-Pro-Phe-NH_2	DBP	86	396	179–181	−68.0(DMF)
9h	*Z*-Val-Ala-OMe	DBP	80	337	162–163 [162.5–163] [17]	−50.0(MeOH) [17] [−49.5(MeOH)]
9i	*Z*-Val-Gly-OEt	DBP	77	337	165–167 [162–164] [18]	−26.5(EtOH) [18] [−27(EtOH)]
9j	*Z*-Val-Phe-NH_2	DBP	88	398	210–212	−32.0(DMF)

[a] Amino acids are of the L configuration unless otherwise indicated.

surement proceeded as Young described. Table 4 shows that the optical purity $(C_L/C_L + C_{DL})\%$ of the model compound was in the range 88–95%.

The degree of racemization could also be detected by ^{31}P NMR techniques; for example, in the previous paper (*9*), we found that the racemic pair of compounds *N*-(diisopropyloxyphosphoryl)-DL-alanine reacted with L-phenylalanine methyl ester hydrochloride to give two diasteroisomers that gave two ^{31}P NMR signals with a difference of 0.1 ppm (4.8 Hz). However, when the optically pure *N*-(diisopropyloxyphosphoryl)-L-alanine was reacted with L-phenylalanine methyl ester hydrochloride using all types of dialkyl phosphites (dimethyl phosphite (DMPH), diethyl phosphite (DEPH), diisopropyl phosphite (DIPPH), and dibutyl phosphate (DBPH)) as coupling reagents, the product **6a** (DIPP-L-Ala-L-Phe-

TABLE 4

Racemization of Coupling Reaction for the Synthesis of the Model Compound Bz-Leu-Gly-OEt (Measured by the Young Method)

Reagent	Condition	Yield (%)	$[\alpha]_D^{30°C}$(EtOH, C = 3.1)	$C_L/C_L + C_{DL}$
DMPH	1 step −5°C 2 h 2 step RT 4 h	78	−31.2	91.8%
DEPH	2 step RT 4 h	85	−32.0	94.1%
DIPPH	2 step RT 4 h	82	−30.0	88.2%
DBPH	2 step RT 4 h	90	−32.4	95.3%

OMe) gave only one ^{31}P NMR signal under the same instrumental conditions, implying that no racemization occurred during this peptide bond formation.

In conclusion, the dialkyl phosphite is an effective activating reagent for peptide bond formation, as well as for the synthesis of amides (compound **10** in Table 1) in general. The present method has the potential for wide application in peptide synthesis because of its availability, stability, and low racemization. The practical execution of the procedure is very simple and the yields are moderate.

EXPERIMENTAL

The ^{13}C NMR, ^{31}P NMR, and ^{1}H NMR spectra were taken on a JEOL FX-100, FT-80, Bruker AM-300, EM-360L 60-MHz spectrometer. The ^{31}P NMR shifts used 85% phosphoric acid as the external reference. The ^{31}P NMR spectra were recorded by the broadband decoupling program. The ^{13}C NMR spectra used chloroform-*d* as the internal reference at 76.9 ppm. TMS was used as the internal standard for the ^{1}H NMR spectra. Positive-ion FAB–MS data were obtained on a KYKY Zhp-5 double-focusing mass spectrometer from the Scientific Instrument Factory (Beijing, China) equipped with a standard KYKY fast atom gun. Infrared spectra were determined with a Carlzeiss Jena Specord 75IR instrument. The optical rotations of the dipeptides were measured with a WZZ polarimeter made by Shanghai Optical Co. (China). The melting points were uncorrected.

*Synthesis of N-(Diisopropyloxyphosphoryl)dipeptide Esters **6a–6g**; N-Benzoyl-leucine–Glycine Ethyl Ester **11**; and N-Benzoyl Butyl Amide **10** Using Dimethyl Phosphite, Diethyl Phosphite, Diisopropyl Phosphite, or Dibutyl Phosphite as the Coupling Reagent: General Procedure*

To a solution of *N*-(diisopropyloxyphosphoryl)amino acid (or *N*-benzoyl amino acid, benzoic acid) (2 mmol) in methylene dichloride (15 ml) (or other organic solvents such as THF or DMF) at 0°C was added 2 eq of triethylamine. The carbon tetrachloride solution (10 ml) containing 1.1 eq of dialky phosphite (DMPH, DEPH, DIPPH, DBPH) was then dropped into it within 10 min. The mixture was stirred at 0°C for 2–4 h. An additional 2 of triethylamine and 1.1 eq of amino acid ester hydrochloride salt were added and stirred at room temperature for a few hours. The final solution was washed with dilute citric acid solution, saturated sodium bicarbonate, and water. The organic layer was dried over anhydrous magnesium sulfate, and after evaporation the residue was purified by recrystallization or chromatographic purification on a silica gel column eluted with ethyl acetate and petroleum ether (Tables 1 and 2). The products could be purified by several washings with petroleum ether.

N-(Diisopropyloxyphosphoryl)-L-alanine–L-phenylalanine methyl ester (***6a***) (*DMPH, DEPH, DIPPH, DBPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 1.0–1.3 (m), 15H, 2.8–3.0 (d), 2H, 3.5–3.6 (s), 3H, 3.6–3.8 (br s), 1H, 4.2–4.8 (m), 4H, 6.8–7.2 (m) 5H, 7.3–7.5 (br s), 1H. *Anal.* Calcd for $C_{19}H_{31}O_6N_2P$: C, 55.04%; H, 7.48%; N, 6.76%. Found: C, 54.66%; H, 7.63%; N, 6.34%.

N-(Diisopropyloxyphosphoryl)-L-alanine–L-tyrosine methyl ester (**6b**) (*DMPH*). ^{1}H NMR (100 MHz, DMSO-d_6): 1.0–2.0 (m), 15H, 2.5–5.5 (m), 10H, 6.3–7.5 (br s), 4H, 7.5–8.5 (br s), 1H, 8.5–9.5 (br s), 1H. *Anal.* Calcd for $C_{19}H_{31}O_7N_2P$: C, 53.02%; H, 7.21%; N, 6.51%. Found: C, 52.92%; H, 7.10%; N, 6.25%.

N-(Diisopropyloxyphosphoryl)-glycine–glycine ethyl ester (**6c**) (*DMPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 1.1–1.9 (m), 15H, 4.2–5.4 (m), 9H, 7.6–7.9 (br s), 1H. *Anal.* Calcd for $C_{12}H_{25}O_6N_2P$: C, 44.44%; H, 7.72%; N, 8.64%. Found: C, 44.95%; H, 7.70%; N, 7.43%.

N-(Diisopropyloxyphosphoryl)-L-phenylalanine–glycine ethyl ester (**6d**) (*DMPH, DEPH, DBPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 1.0–1.4 (m), 15H, 2.8–3.1 (d), 2H, 3.5–4.6 (m), 8H, 7.1–7.2 (s), 5H, 7.2–7.5 (br s), 1H. *Anal.* Calcd for $C_{19}H_{31}O_6N_2P$: C, 55.07%; H, 7.49%; N, 6.76%. Found: C, 55.35%; H, 7.76%; N, 6.81%.

N-(Diisopropyloxyphosphoryl)-L-phenylalanine-L-tyrosine methyl ester (**6e**) (*DMPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 1.1–1.8 (t), 12H, 3.0–3.5 (br s), 4H, 3.8–4.0 (s), 3H, 4.2–5.2 (m), 5H, 6.9–7.1 (s), 4H, 7.3–7.6 (s), 5H, 8.0–8.6 (br s), 1H. *Anal.* Calcd for $C_{25}H_{35}O_7N_2P$: C, 59.29%; H, 6.92%; N, 5.53%. Found: C, 59.04%; H, 7.25%; N, 5.46%.

N-(Diisopropyloxyphosphoryl)-L-proline–glycine ethyl ester (**6f**): (*DMPH, DEPH, DIPPH, DBPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 1.2–1.6 (m), 15H, 1.7–2.5 (m), 4H, 3.2–3.5 (m), 2H, 4.0–5.0 (m), 7H, 7.8–8.0 (br s), 1H. *Anal.* Calcd for $C_{15}H_{29}O_6N_2P$: C, 49.45%; H, 7.97%; N, 7.69%. Found: C, 49.02%; H, 8.18%; N, 8.22%.

N-(Diisopropyloxyphosphoryl)-L-proline–L-tyrosine methyl ester (**6g**): (*DMPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 1.2–1.5 (d), 12H, 1.6–2.2 (br s), 4H, 2.8–3.5 (br s), 4H, 3.6–3.9 (s), 3H, 3.9–5.0 (m), 4H, 6.6–7.1 (q), 4H, 7.1–7.5 (br s), 1H, 7.5–7.9 (br s), 1H. *Anal.* Calcd for $C_{21}H_{33}O_7N_2P$: C, 55.26%; H, 7.24%; N, 6.14%. Found: C, 55.66%; H, 7.19%: N, 6.12%.

Benzoyl butyl amide (**10**) (*DBPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 0.6–1.8 (m), 7H, 3.1–3.5 (br s), 2H, 7.0–8.1 (m), 6H. *Anal.* Calcd for $C_{11}H_{15}O$ N; C, 74.58%; H, 8.47%; N, 7.91%. Found: C, 74.19%; H, 8.30%; N, 7.56%.

Benzoyl-leucine–glycine ethyl ester (**11**) (*DMPH, DEPH, DIPPH, DBPH*). ^{1}H NMR (60 MHz, $CDCl_3$): 0.8–2.1 (m), 12H, 3.8–4.4 (m), 4H, 4.7–5.1 (br s), 1H, 7.2–8.0 (m), 7H.

Synthesis of N-(Diisopropyloxyphosphoryl)-L-phenylalanine–glycine Ethyl Ester (**6d**) *Using Dicyclohexylcarbodiimide or Dicyclohexylcarbodiimide with N-Hydroxysuccinimide as the Coupling Reagent: General Procedure*

To a solution of *N*-(diisopropyloxyphosphoryl)amino acid (2 mmol) in methylene dichloride (30 ml) (or other solvents such as chloroform, THF, and DMF) at −10°C were added 2 eq of *N*-hydroxysuccinimide, 1 eq of amino acid ester hydrochloride salt, 1 eq of triethylamine, and 1.1 eq of dicyclohexylcarbodiimide. The solution was stirred for 2 h at −10°C and then stirred at room temperature overnight. After filtration and evaporation, the residue was dissolved in ethyl acetate

and filtered again. The organic layer was washed with dilute citric acid, saturated sodium bicarbonate, and water. The organic layer was dried over anhydrous magnesium sulfate, and after evaporation a white solid was obtained. Recrystallization from ethyl acetate yielded a white crystal product (Tables 1 and 2). ^{1}H NMR (60 MHz, $CDCl_3$): 1.0–1.4 (m), 15H, 2.8–3.1 (d), 2H, 3.5–4.6 (m), 8H, 7.1–7.2 (s), 5H, 7.2–7.5 (br s), 1H.

Synthesis of N-(Benzyloxycarbonyl)dipeptides ***9a–9j****, Using Dialkyl Phosphite as the Coupling Reagent: General Procedure*

N-(Benzyloxylcarbonyl)amino acid (10 mmol) was dissolved in tetrahydrofuran (or other organic solvents such as chloroform, THF, and DMF) (10 ml) and triethylamine (3 ml), and the solution was cooled in an ice bath (−10°C). To this solution was added dialkyl phosphite (11 mmol) in carbon tetrachloride (3 ml). After the solution was stirred for 1–2 h at low temperature (below −5°C), amino acid ester or amide (10 mmol) in tetrahydrofuran or chloroform (5 ml) was added, and the mixture was stirred below −5°C for 1 h and at room temperature for 2 h. Then triethylamine hydrochloride was filtered off and the solution was evaporated *in vacuo* to dryness. The residue was dissolved in ethyl acetate, and the solution was washed with water, dilute HCl, and water, dried over anhydrous magnesium sulfate, and evaporated *in vacuo* to dryness. In most cases, the product at this stage could be obtained in pure state as detected by thin-layer chromatography and spectroscopic analysis, and satisfactory microanalysis was obtained after one recrystallization (Table 3).

N-(Benzyloxycarbonyl)-L-proline-L-alanine benzyl ester ***(9d)*** *(DBPH). Anal.* Calcd for $C_{23}H_{26}N_2O_5$: C, 67.30%; H, 6.38%; N, 6.805, Found: C, 67.15%; H, 6.29%; N, 6.60%.

N-(Benzyloxycarbonyl)-L-proline–glycine ethyl ester ***(9e)*** *(DBPH). Anal.* Calcd for $C_{17}H_{22}N_2O_5$: C, 61.07%; H, 6.58%; N, 8.35%. Found: C, 61.20%; H, 6.64%; N, 8.27%.

N-(Benzyloxycarbonyl)-L-proline–L-phenylalanine amide ***(9g)*** *(DBPH). Anal.* Calcd for $C_{22}H_{25}N_3O_4$: C, 66.82%; H, 6.37%; N, 10.63%. Found: C, 66.84%; H, 6.34%; N, 10.59%.

N-(Benzyloxycarbonyl)-L-valine-L-phenylalanine amide ***(9j)*****:** *(DBPH). Anal.* Calcd for $C_{22}H_{27}N_3O_4$: C, 66.48%; H, 6.85%; N, 10.57%. Found: C, 66.37%; H, 6.84%; N, 10.42%.

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